II. REMARKS

Claims Amendments

Claims 32, 74-76, and 79 have been amended. Claims 77 and 78 are cancelled without prejudice or disclaimer, and claims 81-83 are newly added. The claims amendments and new claims and are fully supported by the specification and claims as filed and do not introduce new matter. Their entry is respectfully requested.

Claims 77 and 78 have been cancelled without prejudice to advance prosecution of the present application, and Applicants expressly reserve the right to prosecute these claims, or claims based on the same subject matter of either or both of claims 77 and 78, in other applications, such as continuation applications.

The amendment to claim 32 is solely to correct a grammatical error. The amendments to claims 74 and 75 are to clarify that the array has at least 48 spots (claim 74) or at least 90 spots (claim 75) at discrete locations that comprise antibodies. Support for these amendments can be found, for example, in Figure 1, in which each of six antibodies is spotted at a minimum of eight discrete locations on the depicted array to provide at least 48 discrete antibody spots; in Figure 3, which depicts an array having six antibodies spotted in fifteen discrete locations per antibody to provide at least 90 discrete antibody spots; in Figure 4, which depicts an array having six antibodies each of which is spotted in at least thirteen distinct locations to provide at least 78 discrete antibody spots, and, for example, in Figure 5, in which each of eight antibodies is spotted in at least forty-eight locations of the depicted array, to provide at least 384 discrete antibody spots. Claims 76 and 79 have been amended so that they no longer specify that the antibodies recognize a set of 1000 human proteins, but instead recite that the array comprises a collection of 1000 different antibodies, as supported by page 3 of the application as filed, lines 12-14. These amendments add no new matter, and their entry is respectfully requested.

New claim 81 is supported by the specification as filed, for example, at least in Figure 5, in which each of eight antibodies is spotted in at least forty-eight locations of the depicted array, to provide at least 384 discrete antibody spots. New claim 82 is supported by the specification at least in Figure 3, which depicts an array having four antibodies that bind mammalian proteins spotted in fifteen discrete locations per antibody to provide at least 60 discrete spots having antibodies that bind mammalian proteins. New claim 83 is supported by the specification at least in Figure 5, which depicts an array having four antibodies that bind mammalian proteins

spotted in at least 48 discrete locations per antibody to provide at least 192 discrete spots having antibodies that bind mammalian proteins. The new claims add no new matter, and their entry is respectfully requested.

Upon entry of the present amendment, claims 31 to 37, 39, 40, 51, 52, 54-56, and 58-76, and 79-83 will be pending.

Specification Amendments

Applicants have amended the specification, on pages 39-40 to comply with the rules on the use of trademark designations in patent applications.

Applicants have also amended the specification on page 24 to comply with the Sequence Listing requirements of 37 CFR 1.821 through 1.825.

These amendments to the specification add no new subject matter, and Applicants respectfully request entry of these amendments to the specification.

Regarding the Sequence Listing

Provided herewith is a sequence listing in compliance with 37 CFR 1.821 through 1.825. Applicants have also submitted herein an amendment to the specification to comply with the sequence rules, and respectfully request its entry. Applicant were instructed to provide a copy of the Notice to Compy with this response; however, no Notice to Comply was received by Applicants with the Office Action, thus Applicants regret that they are unable to provide a copy of the Notice to Comply.

Claim Rejections under 35 USC § 112

Claims 74-79 have been rejected under 35 USC §112, second paragraph, for being indefinite. Claims 74 and 75, which have been rejected for use of the term antibody "preparations", have been amended herein such that they no longer recite "preparations". Claims 77 and 78 are cancelled without prejudice, rendering their rejection moot. Claims 76 and 79, which have been rejected for use of the expression "a collection of antibodies that recognize a set of 1000 human antigens", have been amended herein such that they now recite " a set of 1000 different antibodies". Applicants assert that claims 74-79 as amended are clear and definite, and therefore respectfully request that the rejection under 35 USC §112, second paragraph, be removed.

Claims 74-80 have been rejected for failing to comply with the written description paragraph of 35 USC §112, first paragraph, for containing subject matter that was not described in the specification, at the time the application was filed, in such a way as to convey to a skilled artisan that the inventors had possession of the claimed invention. Solely to advance prosecution of the application, and not in acquiescence to the rejection, claims 74 and 75 have been amended such that they no longer recite "48 different antibody preparations" and "90 different antibody preparations", respectively. Support for claims 74 and 75 as amended in the specification as filed is provided herein in the section entitled "Claims Amendments". Claims 76 and 79 as amended such that they recite that the array "comprises a collection of 1000 different antibodies". The claims as amended find support on page 3 of the application as filed, lines 12-14 which states: "Recently new technologies have arisen that allow the creation of microarrays containing thousands or millions of different elements.". Claims 77 and 78 have been cancelled without prejudice to advance prosecution of the application, rendering their rejection moot. Support for claim 80 can be found in Example VII of the application as filed, and also in Figures 5A, 5B, and 5C. and in particular lines 8-10, 18-28, and the first and second paragraphs of page 47, which describe the binding of an antigen of the cell lysate (beta galactosidase) to an antibody on the solid surface of the array (the beta galactosidase antibody), as shown in Figures 5A, 5B, and 5C. Applicants assert that claims 74-76, 79, and 80 are in compliance with the written description requirement of 35 USC §112, first paragraph, and respectfully request that the rejection be removed.

Claim Rejections under 35 USC § 103

The rejection of claims 37, 55, 56, 58, 59, 63, 64, and 70-73 under 35 U.S.C. §103(a) as allegedly obvious over Shalon et al. (WO 95/35505) in view of Schuh et al. (J. Immunological Methods, 152:59 1992) is respectfully traversed. To establish a prima facie case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence. The weight to be accorded to the evidence depends on the individual factual circumstances of each case. MPEP 2141; Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

With respect to claims 70-73, Applicants assert that not all elements of the claims are present in the cited art, as neither Shalon et al. nor Schuh et al. teach a solid support having a plurality of bound antibodies that recognize proteins of a first species. Shalon is silent as to the species specificity of antibodies. Schuh discloses microtiter plate immunoabsorption, in which, in one experiment, rat monoclonal antibodies that recognize *human* proteins are used in combination with rat monoclonal antibodies that recognize *mouse* monoclonal antibodies ("capture antibodies" (HB90)) (Schuh et al., page 61, left column, first paragraph on *Membrane antigens* under the heading *Immunoadsorption and ELISA*). In other experiments to detect serum proteins, rat monoclonal antibodies that recognize mouse serum proteins are used in conjunction with rat antibodies that do *not* recognize mouse proteins (e.g.,TmT4, DNP2) (Schuh et al., page 60, right column, third paragraph), or mouse antibodies that recognize human proteins are used in conjunction with rat antibodies that do *not* recognize human proteins (e.g., E6) (Schuh et al., page 60, right column, third paragraph).

Further, the Office Action of August 8, 2006 does not provide any case for motivation or suggestion in the references for combining a microarray, as disclosed in Shalon et al., with

the use of antibodies that recognize proteins of a first species. In fact, an array having a plurality of antibodies at discrete locations, in which the antibodies recognize proteins of a first species is not suggested in the references, nor is any motivation for such a combination provided by the references.

With respect to claims 37, 55, 56, 58, 59, 63, and 64, there is no reasonable expectation of success in combining antibodies of unknown antigen specificity, as disclosed in Schuh, with an array as disclosed in Shalon et al. Further, no motivation or suggestion is present for combining these references.

Schuh teaches immunoabsorption of proteins and their subsequent elution, followed by SDS PAGE and detection of the proteins using Western blotting. There is no teaching in Shalon et al. that a bound antigen could be eluted from an antibody microarray in quantities that could be detected on a gel or blotted membrane, as disclosed in Schuh. An array, as disclosed in Shalon, would not capture sufficient antigen to allow detection on a gel after elution of the antigen; moreover, elution from individual locations of an array surface, as opposed to wells of a microtiter plate, would be at best difficult, and combined with the gel detection methods of Schuh, infeasible. In fact, there is no teaching in Shalon et al. of elution of any biomolecule after immobilization on the microarrays disclosed therein. Finally, there is no teaching in Shalon et al. that even if an antigen could be eluted after binding a bound antibody, that the antigen could be eluted in sufficient quantity to permit detection on a blot after separation by SDS PAGE. The small volumes taught in Shalon et al. (50 nl and preferably 2 pl to 2 nl, Page 16, 7-10) are at most $1/500^{th}$ the 50 ul volume used in Schuh et al. (page 61, left column last full paragraph), and preferably as taught by Shalon et al. over 1000-fold less than the volumes of Schuh et al.

Further, a skilled artisan would not be motivated to combine the teachings of Schuh and Shalon because in Schuh, detection occurs by Western blot of eluted antigen. An array as disclosed in Shalon would, as argued above, be infeasible for immunoabsorption and subsequent elution of antigens for further analysis. With regard to these issues, the MPEP states at 2143.01, Section V:

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

In accordance with this, no suggestion of making such a combination is present in the cited references. Indeed, the purported motivation provided in the Office Action of August 8, 2006 cannot reasonably be construed as motivation to make the combination of a microarray of uncharacterized antibodies. To the contrary, the cited passage from the abstract of Schuh et al. provides rationale for using exactly the methods and compositions disclosed in the cited paper, which does not include an array, much less a microarray having uncharacterized antibodies at discrete locations.

The abstract in fact specifies the use of plates having wells for the study of uncharacterized antibodies in stating: "The amount of bound and removed antigen can be quantitated by developing eluted and non-eluted control wells by ELISA techniques. Since this ELISA can be performed rapidly, only samples which contain sufficient specific material can be selected for electrophoresis and blotting." (third paragraph of the abstract of Schuh et al.) Here, the use of multiple wells (e.g., microtiter plates) is critical, since in the proposed methods, some antibodies are eluted while other "non-eluted control wells" are not. This methodology, as detailed above, is not transferrable to microarrays as they are disclosed in Shalon.

Applicants therefore assert that, in the case of claims 70-73, not all claim limitations are present in the cited art, and that no suggestion or motivation is present for combining Shalon et al. with Schuh et al. to produce a microarray having a plurality of antibodies to proteins of a first species located at discrete locations on a solid surface. Applicants further assert that, in the case of claims 37, 55, 56, 58, 59, 63, and 64, there would have been no reasonable expectation of success in combining a microarray, as disclosed in Shalon, with antibodies of unknown antigen specificity, as disclosed in Schuh et al. Applicants in addition contend that no motivation or suggestion for combining Shalon et al. with Schuh et al. to produce a microarray that includes antibodies of uncharacteized antigen specificity. Thus, the cited references do not render the claimed invention obvious. Applicants therefore respectfully request that the rejection of claims 37, 55, 56, 58, 59, 63, 64, and 70-73 under 35 U.S.C. §103(a) be removed.

Claims 39-40 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Shalon et al. in view of Schuh et al. and further in view of Ragg and Whitlow. This rejection is respectfully traversed.

As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al., nor is their suggestion or motivation to combine references present. Ragg and Whitlow relates to single chain antibody fragments, but are silent as to using an antibody microarray in the method of Schuh et al. Accordingly, Ragg and Whitlow do not make up for the deficiency of Shalon et al. and Schuh et al. Thus, Shalon et al., Schuh et al., and Ragg and Whitlow do not, either alone or in combination, render claims 39-40 obvious. Applicants therefore respectfully request that the rejection of claims 39 and 40 under 35 U.S.C. §103(a) be removed.

Claim 65 stands rejected under 35 U.S.C. §103(a) as obvious over Shalon et al. and Schuh et al., further in view of Kohler et al. The rejection is respectfully traversed. There is no reasonable expectation of success to combine a microarray taught by Shalon et al. with uncharacterized antibodies as allegedly disclosed in Schuh et al. Kohler et al. relates to using hybridomas to produce antibodies, but is silent as to using an antibody microarray in the method of Schuh et al. Accordingly, Kohler et al. does not make up for the deficiency of Shalon et al. and Schuh et al. Thus, Shalon et al., Schuh et al., and Koehler et al. do not, either alone or in combination, render claim 65 obvious. Applicants therefore respectfully request that the rejection of claim 65 under 35 U.S.C. §103(a) be removed.

Claims 77-80 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al. in view of Schuh et al. and further in view of Cahill et al. Applicants respectfully traverse this rejection. Applicants assert that Cahill, published in 2001, is not available as a reference, as claims 77-80 are supported by the application as filed, as detailed in the section on 35 U.S.C. §112 rejections. Applicants therefore respectfully request that the rejection of claims 77-80 under 35 U.S.C. §112 be removed.

Claims 31-33, 36, 51, 52, 54, 60-61, and 67-69 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al. in view of Schuh et al. and further in view of Foster et al. Applicants respectfully traverse this rejection.

Shalon et al. is silent with respect to a kit that includes a first reagent for labeling a cell lysate. As stated above, there is no reasonable expectation of success to combine a microarray

taught by Shalon et al. with a cell lysate labeling reagent as allegedly disclosed in Schuh et al. The method of Schuh et al. requires that antigen bind to an immobilized antibody in a well of a microtiter plate and further requires that bound antigen be eluted from the plate and detected after separation and blotting.

There is no teaching in Shalon et al. that a bound antigen could be eluted in sufficient quantity to be further analyzed. A skilled artisan would not be motivated to combine the teachings of Schuh and Shalon because in Schuh, detection occurs by Western blot of eluted antigen. An array, as disclosed in Shalon, would not capture sufficient antigen to allow detection on a gel after elution of the antigen; moreover, elution from individual locations of an array surface, as opposed to wells of a microtiter plate, would be at best difficult, and combined with the gel detection methods of Schuh, infeasible. In fact, there is no teaching in Shalon et al. of elution of any biomolecule after immobilization on the microarrays disclosed therein. Finally, there is no teaching in Shalon et al. that even if an antigen could be eluted after binding a bound antibody, that the antigen could be eluted in sufficient quantity to permit detection on a blot after separation by SDS PAGE. The small volumes taught in Shalon et al. (50 nl and preferably 2 pl to 2 nl, Page 16, 7-10) are at most $1/500^{th}$ the 50 ul volume used in Schuh et al. (page 61, left column last full paragraph), and preferably as taught by Shalon et al. over 1000-fold less than the volumes of Schuh et al.

In addition to the lack of a prima facie case for obviousness as discussed above, there are secondary factors that must be considered with respect to the patentability of the present invention. For example, commercial success has been achieved with the kit of claim 31 and claims dependent therefrom. In fact, numerous companies have commercialized microarrays and/or kits according to the pending claims (For example, antibody arrays and kits available from Clontech, Montain View, California, clontech.com, used in protein expression profiling service from rzpd, Berlin Germany, www.rzpd.de, Panorama® antibody microarrays and kits, Sigma-Aldrich, sigma-aldrich.com, St. Louis, MO, antibody microarray and expression profiling services from Eurogentec, Inc., San Diego, CA, eurogentec.com, also see Raybio® antibody arrays available from Ray Biotech, Inc. Norcross,GA (www.raybiotech.com), and antibody arrays from Panomics, Inc., Fremont, CA, www.panomics.com). This provides evidence not only of commercial success but also of copying by others. Furthermore, the invention meets the long-felt need of providing tools that make it possible to utilize antibodies

to analyze protein expression for large numbers of proteins and/or samples simultaneously. Thus, the cited references do not render the claimed invention obvious. Applicants therefore respectfully request that the rejection be removed.

Foster et al., relates to enzyme immunoassays and discloses kits, but is silent as to microarrays, reagents for labeling a cell lysate, and using an antibody microarray in the method of Schuh et al. Accordingly, Foster et al. does not make up for the deficiency of Shalon et al. and Schuh et al. The Office Action further asserts with respect to claims 67-69 that Schuh et al. disclose a second reagent for labeling cell lysates. However, the biotin and avidin reagents of Schuh et al. are part of one reagent for labeling the same cell lysate. That is, only the NHS-LC biotin reagent labels a cell lysate, wherein the avidin reagent is used to detect the biotin reagent but not to label a second cell lysate. Claim 67 recites that the second reagent is for labeling a second cell lysate. Thus, Shalon et al., Schuh et al., and Foster et al. do not, either alone or in combination, render claims 31-33, 36, 51, 52, 54, 60-61, and 67-69 obvious. Applicants therefore respectfully request that the rejection of these claims under 35 U.S.C. §103(a) be removed.

Claims 34 and 35 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al., in view of Schuh et al., further in view of Foster et al., and further in view of Ragg and Whitlow. Applicants respectfully traverse this rejection.

As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al. As indicated above, neither Foster et al., nor Ragg and Whitlow, provide a reasonable expectation of success in using a microarray of Shalon et al. in the method of Schuh et al. Accordingly, Foster et al. and Ragg and Whitlow do not make up for the deficiency of Shalon et al. and Schuh et al. Thus, the references do not render obvious dependent claims 34 and 35 which incorporate the language of claim 31. Applicants therefore respectfully request that the rejection of claims 34 and 35 under 35 U.S.C. §103(a) be removed.

Claim 62 has been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al., in view of Schuh et al., further in view of Foster et al., and further in view of Kohler et al. Applicants respectfully traverse this rejection.

As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al. As indicated above, neither Foster et al., nor Kohler et al., provide a reasonable expectation of success in using a microarray of Shalon et al. in the method of Schuh et al. Accordingly, Foster et al. and Kohler et al. do not make up for the deficiency of Shalon et al. and Schuh et al. Thus, the references do not render obvious dependent claim 62. Applicants therefore respectfully request that the rejection of claims 62 under 35 U.S.C. §103(a) be removed.

Response to Examiner's Response to Applicants' Prior Arguments

The Examiner asserts in the Office Action mailed August 8, 2006, that there is no requirement that the prior art must suggest that the claimed product will have the same or similar utility as that discovered by applicant in order to support a conclusion of obviousness and a reasonable expectation of success. The Applicants assert, however, that Shalon et al. in view of Schuh et al. do not provide a reasonable expectation of success with respect to the use of the arrays of Shalon et al. in the method of Schuh et al. because the method of Schuh et al. requires more antigen than a skilled artisan would expect to be present on a microarray.

The Examiner contends that under Dillon (In re Dillon, 919 F.2d 688, 696, 16 USPQ 2d 1897, 1904 (Fed Cir 1990) (en banc), cert. denied, 111S. Ct. 1682 (1991)) an obviousness rejection is proper so long as the prior art suggests a reason or provides a motivation, even where the reason or motivation is different from that discovered by Applicant. The Examiner then goes on to recite advantages allegedly provided in Schuh et al., including the requirement of a minimal amount of antigen. Applicants do not agree.

First, there is no suggestion or reason to combine Schuh et al. and Shalon et al. whatsoever in what the Examiner has cited. Therefore, the Examiner's comment does not apply to the legal conclusion based on the present facts. Furthermore, regarding a suggestion or motivation to modify the references, the proposed modification cannot render the prior art unsatisfactory for its intended purpose. (MPEP 2143.01; In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). Modification of the method of Schuh et al. with a microarray instead of an ELISA plate, renders the method unsatisfactory for its intended purpose, since insufficient antigen would be isolated to perform the method. Therefore, there is no suggestion or motivation to combine the references.

Regarding Schuh et al.'s alleged advantage of requiring only a "minimal amount of antigen," (a claim made in the abstract of Schuh et al., and quoted by the Examiner) a skilled artisan would not conclude from the disclosure of Schuh et al.'s method, that utilizes isolation of proteins from ELISA wells and detection using Western blot, that the method could be successfully employed using microarrays. A skilled artisan would understand that a microarray would not provide sufficient quantity to perform such a method. Accordingly, the amount of antigen isolated using a microarray would be less than the "minimal amount of antigen" that could be successfully analyzed using the method of Schuh et al. According to the Examiner's allegation, Schuh et al. conclude that their method had the advantage of requiring a minimal amount of antigen. As the method was disclosed using ELISA multiwell plates, an artisan would not be motivated then to attempt to use smaller immobilization areas and less antigen.

Regarding the Examiner's comments about Shalon et al. not teaching antibody immobilization, especially with respect to antibodies that retain their ability to bind antigens, the Examiner concedes that the working examples of Shalon et al. do not provide this. However, the Examiner points to the statements in Shalon et al. that such a method could be used with antibodies, and indicates that other art is used to provide the teaching of immobilized antibodies that retain their ability to bind antigens. The obviousness rejection of the Examiner uses Shalon et al. for its alleged teaching of arrays of antibodies, however. Therefore, the Examiner is relying on the method of Shalon et al. for its immobilization methods, which impliedly are conceded by the Examiner as not teaching immobilization of antibodies that retain their ability to bind antigen.

Regarding the evidence of secondary factors, the Examiner summarily indicates that the evidence of secondary factors provided by the Applicant in the present application are not persuasive because the claimed invention allegedly "would flow logically from the teaching of the prior art." The conclusion by the Examiner in this situation is insufficient to meet the legal requirement that the Examiner must consider the secondary factors that are presented. MPEP 2141; Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983);

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). In fact, since every obviousness rejection is in essence an argument that the invention would flow logically from the teaching of the prior art, if the Examiner's legal analysis is proper, secondary factors would never be considered. Rather, the Examiner must consider the evidence of significant commercial success, long-felt need, and copying of others that have been presented in the present Amendment.

Conclusion

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

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